Detailed Action

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The amendment and Remarks, submitted 4 February 2011, have been entered and considered. Claims 1, 3, 4, 6, 10-12, 19-24 and 26-36 are pending. Claims 2, 5, 7-9, 13-18 and 25 have been cancelled. Claims 1, 3, 4, 23, 24, 26, 27 and 36 have been amended.

Claims 1, 3, 4, 6, 10-12, 19-24 and 26-36 are under examination in the Instant Application.

Withdrawn Claim Rejections/Objections

Claim Rejections: Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 22 and 23 on the grounds of nonstatutory obviousness-type double patenting over claims 103 and 104 of copending Application No. 2009/0215691 (serial No. 12/335,328), is *withdrawn*, based on claim amendments in the co-pending application.

Maintained Claim Rejections/Objections

Claim Rejections - 35 USC § 112, first paragraph – Scope of Enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1, 3, 4, 6, 10-12, 19-21, 24 and 26-34 remain rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method of promoting regeneration or survival of dopaminergic neurons in mammals injected with the toxin 6-OHDA, by administering soluble NgR1 intracranially, does not enable a method of promoting regeneration or survival of dopaminergic neurons in a mammal in which dopamine neurons have

died from a degenerative disease, or in which NgR1 antagonists other than sNgR1 (amino acids 26 to 310 or 344 of SEQ ID NO: 4) are administered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification does not reasonably provide enablement for an all-encompassing method of promoting regeneration or survival of dopaminergic neurons in a mammal by administering an antagonist of NgR1 other than sNgR1 (SEQ ID NO: 3, 4, 5 or 6), or by any route of administration other than directly into the brain *at the site of injury*. The claims, however, embrace all methods of promoting restoration of dopamine neurons after any injury in the brain involving dopamine neurons, including those involved in human diseases such as Parkinson's disease. Claims 1, 3, 4, 6, 10-12, 19-21, 24 and 26-34 embrace methods of promoting restoration of dopamine neurons after any injury in the brain involving the dopaminergic system and including conditions in which dopaminergic neurons have died and cannot therefore regenerate or be saved.

Experiments presented in the specification show that NOGO1 receptor (NgR1) knockout mice display fewer lost neurons when injected with 6-OHDA (a toxin that specifically targets dopaminergic neurons throughout the brain). The inventors used conventional tests of dopaminergic cell number and function, such as tyrosine hydroxylase staining, as well as movement studies in which the 6-OHDA is injected into one side of the striatum only, and the rats' rotational biases toward the contralateral side are measured after amphetamine administration. However, the claims also embrace methods of treating all dopaminergic brain disorders, using modified analogs of sNgR1, in addition to the known soluble receptor

sequences. The claims also encompass methods of treating diseases that involve dopamine cell apoptosis or degeneration, including those that are not confirmed as involving the NgR1 receptor or any NOGO receptor, and those that stem from permanent dopaminergic cell loss.

In addition, the instant Application also does not reasonably provide enablement for use of variants of NgR1, such as amino acids 26-310 of SEQ ID NO: 3 with *up to ten conservative amino acid substitutions*, as recited in claim 6. Although amino acids 26-310 and 26 to 344 of SEQ ID NO: 1, have been shown to act as soluble forms of NgR1, and appear to act as antagonists at NOGO receptors, no variants of sNgR1 were made or used in any of the experiments described.

Applicants argue:

"The Examiner's main argument in support of the rejection is that the 6-OHDA model described in Examples 1 and 2 of the specification, which was used in rats and in Nogo receptor knockout mice to demonstrate a link between Nogo receptor and dopaminergic neuronal degeneration, does not sufficiently enable the skilled artisan to practice the invention without undue experimentation"

(Remarks, 16 August 2010, p. 10).

Applicants' arguments filed 16 August 2010 have been fully considered but they are not persuasive for the following reasons:

The first paragraph of 35 USC § 112 requires that the enabling specification must teach those skilled in the art how to make and use the claimed invention without undue experimentation. Case law confirms that the disclosure of a patent application must enable the invention: "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." (Wands', 858 F.2d at 736-37, 8 USPQ2d at 1404; In re Fisher, 427 F.2d 833,839, 166 USPQ 18,

24 (CCPA 1970)) and: "the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification" (In re Wright (CAFC) 27 USPQ2d 1510 at 1513). Thus, case law supports the examiner's position that the instant disclosure is not sufficient to enable the invention without "undue experimentation." For example, it is not known how experiments with NOGO-knockout mice could provide evidence to support a method of treatment of human beings with neurodegenerative diseases. The nexus between the knockout mice and a role for NOGO *in Parkinson's disease* and other neurodegenerative diseases is tenuous at best and would be made more clear if there were more experimentation that at least addressed that issue. In addition, while it is generally assumed that adding a soluble receptor will competitively bind ligands for the receptor, thus acting indirectly as an "antagonist," it is not at all clear-cut that any antibodies or antibody fragments would display the same function (referring to claims 24-34).

Applicants also argue that:

"Applicants respectfully submit that the reasons for the rejection, as set forth in the Office Action, are insufficient to establish a prima facie case of non-enablement"

and cite In re Wands (858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)) and In re Wright (CAFC) 27 USPQ2d 1510 at 1513 (16 August 2010, p. 12).

Applicant's arguments have been fully considered but are not persuasive for the following reasons:

The first paragraph of 35 USC § 112 requires that the enabling specification must teach those skilled in the art how to make and use the claimed invention without undue experimentation. The examiner agrees that one need not supply information that is well known in the art. However, administration of a NOGO antagonist to treat any dopaminergic

neurodegenerative disease is not a well-known process. Thus, there is little evidence from the literature that NOGO is involved in the etiology of "dopaminergic neuronal degeneration" (claim 1), or responsible for poor outcomes in neurodegenerative diseases when attempts are made at treatment. In other words, there is no evidence that NOGO is involved in the inability of dopaminergic neurons to regenerate after injury. The examiner also agrees that the 6-OHDA model of selective dopaminergic ablation is a valid experimental model that focuses on destruction only of dopaminergic cells. However, it is not a valid model that mimics all or many neurodegenerative diseases that would fall into the genus of those that would be covered by the claimed method.

As far as whether the claimed *variants* of sNgR1 are enabled, as described in claim 6, applicants assert that it would be routine in the art to simply make and test all or many of the variants claimed:

> "Once obtained, the soluble NgR1 polypeptides with up to ten conservative amino acid substitutions could be tested in the 6-OHDA animal model provided in the Examples for the ability to promote regeneration or survival of dopaminergic neurons. Such testing, as discussed above, would be considered to be routine"

(Remarks, p. 17).

The examiner agrees that it is routine in the art to mutate the coding sequence of any polypeptide in order to generate any variant possible. However, it would require undue experimentation to make and test enough examples of polypeptides with "up to ten amino acid substitutions." There is not enough experimental evidence that polypeptides with up to ten substitutions function just like the sNgR1 represented by SEQ ID NO: 3, 4, 5 or 6, such that the genus is enabled and the newly-made variants inhibit NOGO receptor-mediated activity with the same affinity and specificity as the soluble receptor antagonists described in the specification.

Claim Rejections - 35 USC § 112, first paragraph – Lack of Enablement

Claims 22, 23, 35 and 36 *remain* rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The rejection was made previously (14 April 2010) because the instant specification does not reasonably provide enablement for a method of promoting regeneration or survival of dopaminergic neurons in a subject with **Parkinson's** disease by administering an antagonist of NgR1, including antibodies, and including antagonists from the soluble receptor sNgR1. The examiner agrees that clinical efficacy of the claimed methods is not a requirement of enablement (Remarks, p. 18).

The examiner contends that the specification is not enabling for claims 22, 23, 35 and 36, because applicants have failed to demonstrate a nexus between Parkinson's disease and NgR1, such that administration of sNgR1 will slow or reverse the loss of cells in the substantia nigra. In addition, methods of treatment, even if performed in animals, must be sufficiently described such that undue experimentation is unnecessary. There is no data showing that the soluble NgR1 receptor is effective in treating a patient with Parkinson's disease or even an animal model of Parkinson's disease. Applicants fail to teach how to use sNgR1 to treat patients or subjects, along with guidance as to the route, duration, and quantity of administration of the disclosed sNgR1 to a subject; such information is not provided by the instant specification. The instant specification also fails to disclose how these parameters are to be determined, how a similar product was practiced in the art, or to provide even a single working example of the sNgR1 ligand being used to treat Parkinson's disease. In the absence of just such guidance, a practitioner would have to resort to a substantial amount of undue experimentation involving the compositions, variations in

the amounts, the mechanics of administration deep into the brain, and the duration of administration of the recited ligands in order to determine whether the claimed product is effective in treating Parkinson's disease.

Applicants argue:

"In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are."

(Remarks, p. 19).

The examiner agrees, and the courts have upheld, that all that is required to enable an invention, is a reasonable correlation between the activity and the asserted use (Nelson v. Bowler, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980)). The examiner has determined in the instant case that an example of induced cell loss, caused by a toxin (6-OHDA), does not provide a reasonable level of evidence to enable in vivo use of the NgR1 polypeptide in order to treat Parkinson's disease.

Conclusion: Claims 1, 3, 4, 6, 10-12, 19-24 and 26-36 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/

31 May 2011

/Dong Jiang/
Primary Examiner, Art Unit 1646